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FILE 'MEDLINE, CAPLUS, BIOSIS, SCISEARCH' ENTERED AT 18:48:32 ON 03 MAY 2004

L1 43 S (HERV OR HUMAN(W)ENDOGENOUS(W)RETROVIR?)(4A)(PROMOTER OR PROM
L2 22 DUP REM L1 (21 DUPLICATES REMOVED)

=> d au ti so ab 1-22 l2

L2 ANSWER 1 OF 22 CAPLUS COPYRIGHT 2004 ACS on STN
AU Cheng, You-Hong; Richardson, Brian D.; Hubert, Michael A.; Handwerger, Stuart
TI Isolation and characterization of the human syncytin gene promoter
SO Biology of Reproduction (2004), 70(3), 694-701
CODEN: BIREBV; ISSN: 0006-3363
AB Syncytin, a protein encoded by an envelope gene of a human endogenous retrovirus-W (HERV-W), plays a critical role in trophoblast differentiation. We isolated the 5'-flanking region of the syncytin gene from human genomic DNA by PCR and identified cis-acting elements on the promoter that are important for transcription. The major transcription initiation site identified by mung bean nuclease protection assays is 56 base pairs (bp) downstream from a putative CCAAT box. Deletion anal. of the 5'-flanking region of the syncytin gene indicated that the proximal 148 bp are essential for minimal promoter activity and that regions of the promoter from nt -1519 to -984 and nt -294 to -148 are required for maximal expression in normal trophoblast cells. DNase I footprint anal. of the region between nt -252 and +110 revealed three protected regions, FP1-FP3. Mutagenesis of a hepatocyte-specific nuclear protein-1 (HAPF1) binding site in FP1 and a TATA box in FP3 had no effects on basal promoter activity. However, mutation of the CCAAT motif and the octamer protein (Oct) binding site in FP2 decreased promoter activity by 88% and 76%, resp. Mutation of the ecdysone receptor (EcR) response element in FP2, which may bind a nuclear hormone receptor, increased basal promoter activity by 2-fold. Gel shift and supershift assays indicated that CCAAT-binding factor (CBF) binds to the CCAAT motif and that Oct binds to the Oct binding site. Taken together, these findings indicate that the syncytin promoter is located in the 5' long terminal repeat (LTR) of the HERV-W gene and that binding sites for CBF and Oct in the proximal promoter are critical for transcriptional regulation of the gene in trophoblast cells.

L2 ANSWER 2 OF 22 CAPLUS COPYRIGHT 2004 ACS on STN
AU Dunn, Catherine A.; Medstrand, Patrik; Mager, Dixie L.
TI An endogenous retroviral long terminal repeat is the dominant promoter for human β1,3-galactosyltransferase 5 in the colon
SO Proceedings of the National Academy of Sciences of the United States of America (2003), 100(22), 12841-12846
CODEN: PNASA6; ISSN: 0027-8424
AB LTRs of endogenous retroviruses are known to affect expression of several human genes, typically as a relatively minor alternative promoter. Here, we report that an endogenous retrovirus LTR acts as one of at least two alternative promoters for the human β1,3-galactosyltransferase 5 gene, involved in type 1 Lewis antigen synthesis, and show that the LTR promoter is most active in the gastrointestinal tract and mammary gland. Indeed, the LTR is the dominant promoter in the colon, indicating that this ancient retroviral element has a major impact on gene expression. Using colorectal cancer cell lines and electrophoretic mobility-shift assays, we found that hepatocyte nuclear factor 1 (HNF-1) binds a site within the retroviral promoter and that expression of HNF-1 and interaction with its binding site correlated with promoter activation. We conclude that HNF-1 is at least partially responsible for the

tissue-specific activation of the LTR promoter of human β1,3-galactosyltransferase 5. We demonstrate that this tissue-specific transcription factor is implicated in the activation of an LTR gene promoter.

L2 ANSWER 3 OF 22 CAPLUS COPYRIGHT 2004 ACS on STN
AU Ling, Jianhua; Pi, Wenhu; Yu, Xiuping; Bengra, Chikh; Long, Qiaoming; Jin, Huaqian; Seyfang, Andreas; Tuan, Dorothy
TI The ERV-9 LTR enhancer is not blocked by the HS5 insulator and synthesizes through the HS5 site non-coding, long RNAs that regulate LTR enhancer function
SO Nucleic Acids Research (2003), 31(15), 4582-4596
CODEN: NARHAD; ISSN: 0305-1048
AB A solitary long terminal repeat (LTR) of ERV-9 human endogenous retrovirus is located upstream of the HS5 site in the human β-globin locus control region and possesses unique enhancer activity in erythroid K562 cells. In cells transfected with plasmid LTR-HS5-εp-GFP, the LTR enhancer activates the GFP reporter gene and is not blocked by the interposed HS5 site, which has been reported to have insulator function. The LTR enhancer initiates synthesis of long RNAs from the LTR promoter through the intervening HS5 site into the ε-globin promoter and the GFP gene. Synthesis of the sense, long LTR RNAs is correlated with high level synthesis of GFP mRNA from the ε-globin promoter. Mutations of the LTR promoter and/or the ε-globin promoter show that (i) the LTR enhancer can autonomously initiate synthesis of LTR RNAs independent of the promoters and (ii) the LTR RNAs are not processed into GFP mRNA or translated into GFP. However, reversing the orientation of the LTR in plasmid (LTR)rev-HS5-εp-GFP, thus reversing the direction of synthesis of LTR RNAs in the antisense direction away from the ε-globin promoter and GFP gene drastically reduces the level of GFP mRNA and thus LTR enhancer function. The results suggest that the LTR-assembled transcription machinery in synthesizing non-coding, LTR RNAs can reach the downstream ε-globin promoter to activate transcription of the GFP gene.

L2 ANSWER 4 OF 22 CAPLUS COPYRIGHT 2004 ACS on STN
AU Bieche, Ivan; Laurent, Anne; Laurendeau, Ingrid; Duret, Laurent; Giovangrandi, Yves; Frendo, Jean-Louis; Olivi, Martine; Fausser, Jean-Luc; Evain-Brion, Daniele; Vidaud, Michel
TI Placenta-specific INSL4 expression is mediated by a human endogenous retrovirus element
SO Biology of Reproduction (2003), 68(4), 1422-1429
CODEN: BIREBV; ISSN: 0006-3363
AB The human insulin-family genes regulate cell growth, metabolism, and tissue-specific functions. Among these different members, only INSL4 gene shows a predominant placenta-specific expression. Here, we show that the human INSL4 gene is tightly clustered with three other members of the human insulin superfamily (RLN1, RLN2, and INSL6) within a 176-kilobase genomic segment on chromosome region 9p23.3-p24.1. We also report evidence that INSL4 is probably the only insulin-like growth factor gene to be primate-specific. We identified an unexpected human endogenous retrovirus (HERV) element inserted into the human INSL4 promoter with a sequence similar to that of env gene, flanked by two long terminal repeats(LTRs). The emergence of INSL4 gene and genomic insertion of HERV appear to have occurred after the divergence of New World and Old World monkeys (.apprx.45 million years ago). Transient transfection expts. showed that the placenta-specific expression of INSL4 is mediated by the 3' LTR of the HERV element, and that the latter may have a major role in INSL4 up-regulation during human cytotrophoblast differentiation into syncytiotrophoblast. Finally, we identified an INSL4 alternatively spliced mRNA species that encodes putative novel INSL4-like peptides. These data support the view that ancient retroviral infection may have been a major event in primate evolution, especially in the functional evolution of the human placenta.

L2 ANSWER 5 OF 22 CAPLUS COPYRIGHT 2004 ACS on STN
AU Tanaka, Satoshi; Ikeda, Hitoshi; Otsuka, Noriyuki; Yamamoto, Yukiyo; Sugaya, Toshiaki; Yoshiki, Takashi
TI Tissue Specific High Level Expression of a Full Length Human Endogenous Retrovirus Genome Transgene, HERV-R, Under Control of its Own Promoter in Rats
SO Transgenic Research (2003), 12(3), 319-328
CODEN: TRSEES; ISSN: 0962-8819
AB Human endogenous retrovirus-R (HERV-R) is one of a full length HERV with a long open reading frame in the env region. The env transcripts are expressed in various human tissues. To investigate the biol. role of HERV-R in vivo, we established two lines of transgenic rats carrying a full sequence of HERV-R under control of its own long terminal repeat (LTR) promoter. One line with tandem integration of multiple copies of the transgene expressed HERV-R mRNA in various organs with different expression levels and relatively higher in Harderian and submandibular salivary glands. In another line, the transgene was integrated as a single copy in a haploid and the expression was detected only in Harderian and submandibular salivary glands. In the placenta, one of the tissues with high levels of the HERV-R expression in humans, the transcription was evident starting the 12th day after gestation. A rabbit antiserum against synthetic peptides corresponding with the HERV-R env gene sequence led to detection of an 85 kDa product as a glycoprotein in the Harderian glands. While no pathol. significance was observed in either line, the transgenic rat may prove to be a suitable model for analyzing the role of HERV-R function in vivo.

L2 ANSWER 6 OF 22 MEDLINE on STN DUPLICATE 1
AU Landry Josette-Renee; Rouhi Arefeh; Medstrand Patrik; Mager Dixie L
TI The Opitz syndrome gene Mid1 is transcribed from a **human endogenous retroviral promoter**.
SO Molecular biology and evolution, (2002 Nov) 19 (11) 1934-42.
Journal code: 8501455. ISSN: 0737-4038.
AB Human endogenous retroviruses (HERVs) and other long terminal repeat (LTR)-containing elements comprise a significant portion (8%) of the human genome and are likely vestiges of retroviral infections during primate evolution. Many of the HERVs present in human DNA have retained functional promoter, enhancer, and polyadenylation signals, and these regulatory sequences have the potential to modify the expression of nearby genes. To identify retroviral elements that contribute to the transcription of human genes, we screened sequence databases for chimeric (viral-cellular) transcripts. These searches revealed a fusion transcript containing the LTR of an HERV-E element linked to the Opitz syndrome gene Mid1. We confirmed the authenticity of the chimeric transcript by 5' rapid amplification of cDNA ends (RACE) and established that the Mid1 mRNA isoform was transcribed from a retroviral LTR. The identification of a retroviral first exon suggested the existence of alternative promoters for Mid1 because nonretroviral (native) 5' untranslated regions (UTRs) had been reported previously for this gene. Although Mid1 transcripts could be detected in all tissues tested, quantitative real-time reverse transcription-polymerase chain reaction indicated that the retroviral promoter contributes significantly to the level of Mid1 transcripts in placenta and embryonic kidney, where chimeric mRNAs were found to represent 25% and 22% of overall Mid1 mRNAs, respectively. Transient transfection studies supported a role for the LTR as a strong tissue-specific promoter in placental and embryonic kidney cell lines and suggested a function for the LTR as an enhancer. These findings provide further evidence that some endogenous retroviruses have evolved a biological function by contributing transcriptional regulatory elements to cellular genes.

L2 ANSWER 7 OF 22 MEDLINE on STN DUPLICATE 2
AU Patzke Sebastian; Lindeskog Mats; Munthe Else; Aasheim Hans Christian

TI Characterization of a novel human endogenous retrovirus, HERV-H/F, expressed in human leukemia cell lines.
SO Virology, (2002 Nov 10) 303 (1) 164-73.
Journal code: 0110674. ISSN: 0042-6822.
AB We have identified and characterized a human endogenous retrovirus (HERV) gag transcript in the human pre-B cell leukemia line Reh. The transcript was found to be a splice product of a structurally intact HERV element located on chromosome 6q13. Its primer binding site is complementary to phenylalanine (F) tRNA, common for the HERV-F family, but the overall genome sequence is closely related to the HERV-H family. The retroviral sequence was therefore designated HERV-H/F. The HERV element shows a distinct mRNA expression pattern among hematopoietic cancer cell lines with expression in some leukemia-derived cell lines of B-lymphoid and myeloid origin. No expression was observed in normal human tissues, indicating a cancer-specific expression pattern. The 5' long terminal repeat (LTR) was tested for **promoter** activity in **HERV** -H/F expressing and nonexpressing cell lines. The cell specificity of the LTR-mediated reporter gene expression did not conclusively correlate with endogenous virus expression, indicating that the transcription regulation of this gene is not alone dependent on cell-specific activity of transcription factors.

L2 ANSWER 8 OF 22 MEDLINE on STN DUPLICATE 3
AU Schon U; Seifarth W; Baust C; Hohenadl C; Erfle V; Leib-Mosch C
TI Cell type-specific expression and **promoter** activity of **human endogenous retroviral** long terminal repeats.
SO Virology, (2001 Jan 5) 279 (1) 280-91.
Journal code: 0110674. ISSN: 0042-6822.
AB Evolution over millions of years has adapted several thousand copies of retrovirus-like elements and over 10 times as many solitary long terminal repeats (LTRs) to their present location in the human genome. Transcription of these human endogenous retroviruses (HERVs) has been detected in various cells and tissues, and in some cases their transcriptional control elements have been recruited by cellular genes. We used a retroviral pol-specific expression array to obtain a HERV transcription profile in a variety of human cells such as epidermal keratinocytes, liver cells, kidney cells, pancreatic cells, lymphocytes, and lung fibroblasts. This rapid screening test revealed a distinct HERV pol-expression pattern in each cell type tested so far. About 40 different U3/R regulatory sequences from the HERV-H and HERV-W families were then amplified from actively transcribed 3'HERV LTRs of various cell lines and tissues. Their promoter activities were compared with LTR sequences of other known HERV families in 12 human cell lines using a transient luciferase reporter system. Expression of the isolated HERV LTRs varied significantly in these cell lines, in some cases showing strict cell type specificity. These results suggest that endogenous retroviral LTRs may be a valuable source of transcriptional regulatory elements for the construction of targeted retroviral expression vectors.

L2 ANSWER 9 OF 22 CAPLUS
IN Leib-Mosch, Christine; Schon, Ulrike; Baust, Corinna
TI Cell-specific retroviral expression vectors carrying the long terminal repeats of human endogenous retroviruses
SO PCT Int. Appl., 67 pp.
CODEN: PIXXD2
AB Retroviral expression vectors using cell-specific promoters are described for, inter alia, the cell-specific expression of therapeutic genes in gene therapy. The invention specifically relates to retroviral expression vectors containing at least the following elements, in a functional configuration: a packaging signal for the vector RNA and for the cell-specific expression of genes; one or more genes under control of a cell-specific **promoter** of a **human endogenous**

retrovirus (HERV). A series of human endogenous retrovirus long terminal repeats were used to drive the expression of a reporter gene in a number of different cell lines. Promoters showed patterns of cell-specificity in cell lines. Introduction of the LTR of of HERV-H6 into mouse mammary tumor virus (MMTV) drove expression of the reporter gene. Expression was not induced by dexamethasone but it showed a 10-fold higher level of expression of the reporter gene than was found in dexamethasone-responsive cells using the MMTV LTR to drive expression. Further anal. of the promoters is described.

L2 ANSWER 10 OF 22 MEDLINE on STN DUPLICATE 4
AU Schulte A M; Malerczyk C; Cabal-Manzano R; Gajarsa J J; List H J; Riegel A T; Wellstein A
TI Influence of the human endogenous retrovirus-like element HERV-E.PTN on the expression of growth factor pleiotrophin: a critical role of a retroviral Sp1-binding site.
SO Oncogene, (2000 Aug 17) 19 (35) 3988-98.
Journal code: 8711562. ISSN: 0950-9232.
AB Germ line insertion of a human endogenous retrovirus-like element (HERV-E.PTN) into the growth factor pleiotrophin (PTN) gene generated a phylogenetically new promoter driving the expression of functional HERV-PTN fusion transcripts. Here we show by in situ hybridization, that HERV-PTN fusion transcripts are expressed in malignant trophoblasts (i.e. choriocarcinoma) and in the proliferative and in the invasive trophoblasts of gestational trophoblastic tissue. Additionally, a 1.9 kb fragment of the **HERV**-derived PTN **promoter** was analysed which has strong activity when transiently transfected into choriocarcinoma JEG-3 cells in contrast to HeLa cells. Deletion of the retrovirally-derived promoter portion abolished its activity and an enhancer (+443 to +486) was identified in this region. Electrophoretic mobility shift and supershift experiments identified a Sp1 binding site in this enhancer and site specific mutation of this site abolished its activity in choriocarcinoma cells. Sp1 overexpression in Drosophila SL2 cells showed that the enhancer activity is mediated via Sp1 binding in vivo. Furthermore, mutation of the Sp1 binding site reduced the activity of a promoter test fragment in choriocarcinoma cells by 80%. Our result shows that a retroviral Sp1 binding site in the PTN promoter is important for the expression of growth factor pleiotrophin in human choriocarcinoma cells. Oncogene (2000) 19, 3988 - 3998.

L2 ANSWER 11 OF 22 CAPLUS COPYRIGHT 2004 ACS on STN
AU Domansky, A. N.; Kopantzev, E. P.; Snezhkov, E. V.; Lebedev, Y. B.; Leib-Mosch, C.; Sverdlov, E. D.
TI Solitary HERV-K LTRs possess bi-directional promoter activity and contain a negative regulatory element in the U5 region
SO FEBS Letters (2000), 472(2,3), 191-195
CODEN: FEBLAL; ISSN: 0014-5793
AB Reporter gene anal. of HERV-K solitary long terminal repeats (LTRs) showed that they retain detectable activity in human teratocarcinoma cells, and can direct the transcription in both orientations relative to the reporter gene. Deletion anal. demonstrated the possible existence of alternative promoters within the LTR as well as a silencer-like element in the U5 region. The results indicate also that all-trans-retinoic acid is capable of modulating expression of the reporter gene directed by a HERV-K LTR in NT2/D1 cells.

L2 ANSWER 12 OF 22 MEDLINE on STN DUPLICATE 5
AU Hohenadl C; Germaier H; Walchner M; Hagenhofer M; Herrmann M; Sturzl M; Kind P; Hehlmann R; Erfle V; Leib-Mosch C
TI Transcriptional activation of endogenous retroviral sequences in human epidermal keratinocytes by UVB irradiation.
SO Journal of investigative dermatology, (1999 Oct) 113 (4) 587-94.
Journal code: 0426720. ISSN: 0022-202X.
AB Ultraviolet radiation is a pathogenic factor in various diseases, e. g.,

autoimmune disorders such as lupus erythematosus. On the other hand, endogenous retroviruses are discussed as etiologic agents in lupus erythematosus. Therefore, we investigated the influence of ultraviolet irradiation on expression of human endogenous retroviral sequences and **human endogenous retroviral** sequence **promoter**-driven transcription of cellular genes using human epidermal keratinocytes as a model system. First, conserved sequences of endogenous retroviral pol genes were amplified from cellular mRNA by reverse transcriptase polymerase chain reaction with degenerate oligonucleotide primers. Polymerase chain reaction products were hybridized in a reverse dot blot hybridization assay to a representative number of distinct cloned human endogenous retroviral pol fragments. Using this method, we could show that irradiation with 30 mJ per cm2 ultraviolet B activates transcription of various endogenous retroviral pol sequences in primary epidermal keratinocytes as well as in a spontaneously immortalized keratinocyte cell line (HaCaT). Interestingly, some of these sequences were found to be closely related to pol sequences of human endogenous retroviral sequences which have been shown to be expressed in autoimmune patients. Analysis of human endogenous retroviral pol expression in vivo using skin biopsies of lupus erythematosus patients revealed similar activation patterns. In a second approach, ultraviolet B- induced chimeric transcripts were isolated which are initiated by **human endogenous retroviral promoters** and proceed into cellular sequences using a newly established modified differential display polymerase chain reaction technique. The activation of human endogenous retroviral sequence transcription by ultraviolet B may contribute to the pathogenesis of lupus erythematosus, where inappropriate antigenic presentation of ultraviolet B-induced viral and cellular proteins could stimulate autoantibody production.

L2 ANSWER 13 OF 22 CAPLUS COPYRIGHT 2004 ACS on STN
AU Fanning, Tom; Alves, Gilda
TI A family of repetitive DNA sequences in Old World primates
SO Gene (1997), 199(1-2), 279-282
CODEN: GENED6; ISSN: 0378-1119
AB A dispersed family of repetitive DNA sequences that is amplified in Old World primates has been characterized. The sequences are present in about 250-350 copies in humans, found on all chromosomes, and some are at least 1 kb in size. Within the core repeat is a 178-bp region that is moderately-to-highly conserved. A representative sequence exhibited strong promoter activity when placed in front of a promoterless gene and transfected into human cells. This promoter activity has been localized to a 138-bp region of the repeat that is about 150 bp downstream of the 178-bp conserved region. Transcripts of the sequences were not detected in six human breast epithelial and teratocarcinoma cell lines. Based upon the work of Pavelitz et al. [Pavelitz, T., Rusche, L., Matera, A.G., Scharf, J.M., Weiner, A.M., 1995. EMBO J. 14, 169-177], the sequence appears to be related to the LTR of an HERV-K class human endogenous retrovirus.

L2 ANSWER 14 OF 22 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
AU Schoen, U. [Reprint author]; Baust, C.; Hohenadl, C. [Reprint author]; Erfle, V. [Reprint author]; Hehlmann, R.; Leib-Moesch, C. [Reprint author]
TI Tissue specific expression and **promoter** activity of different **HERV**-LTRs.
SO Journal of Molecular Medicine (Berlin), (1997) Vol. 75, No. 7, pp. B228. Meeting Info.: XIX Symposium of the International Association for Comparative Research on Leukemia and Related Diseases. Heidelberg, Germany. July 13-18, 1997.
ISSN: 0946-2716.

L2 ANSWER 15 OF 22 CAPLUS COPYRIGHT 2004 ACS on STN
AU Mold, David E.; Wu, Tzyy Choou; Askin, Frederic; Huang, Ru Chih C.
TI Four classes of HERV-K long terminal repeats and their relative promoter

strengths for transcription
SO Journal of Biomedical Science (Basel) (1997), 4(2/3), 78-82
CODEN: JBCIEA; ISSN: 1021-7770
AB Conserved nucleotide sequence variations in the U3 region of the human endogenous retrovirus (HERV)-K 3' long terminal repeats (LTR) were used to distinguish between individual HERV-K proviruses. Four major classes of HERV-K LTRs were identified. HERV-K U3 regions from the different classes were compared in an in vitro transcription assay and were found to vary in their promoter activities.

L2 ANSWER 16 OF 22 MEDLINE on STN DUPLICATE 6
AU Schulte A M; Lai S; Kurtz A; Czubayko F; Riegel A T; Wellstein A
TI Human trophoblast and choriocarcinoma expression of the growth factor pleiotrophin attributable to germ-line insertion of an endogenous retrovirus.
SO Proceedings of the National Academy of Sciences of the United States of America, (1996 Dec 10) 93 (25) 14759-64.
Journal code: 7505876. ISSN: 0027-8424.
AB Retroviral elements are found in abundance throughout the human genome but only rarely have alterations of endogenous genes by retroviral insertions been described. Herein we report that a human endogenous retrovirus (HERV) type C is inserted in the human growth factor gene pleiotrophin (PTN) between the 5' untranslated and the coding region. This insert in the human genome expands the region relative to the murine gene. Studies with promoter-reporter constructs show that the HERV insert in the human PTN gene generates an additional promoter with trophoblast-specific activity. Due to this **promoter** function, fusion transcripts between **HERV** and the open reading frame of PTN (HERV-PTN) were detected in all normal human trophoblast cell cultures as early as 9 weeks after gestation (n = 7) and in all term placenta tissues (n = 5) but not in other normal adult tissues. Furthermore, only trophoblast-derived choriocarcinoma cell lines expressed HERV-PTN mRNA whereas tumor cell lines derived from the embryoblast (teratocarcinoma) or from other lineages failed to do so. We investigated the significance of HERV-PTN mRNA in a choriocarcinoma model by targeting this transcript with ribozymes and found that the depletion of HERV-PTN mRNA prevents human choriocarcinoma growth, invasion, and angiogenesis in mice. This suggests that the tissue-specific expression of PTN due to the HERV insertion in the human genome supports the highly aggressive growth of human choriocarcinoma and possibly of the human trophoblast.

L2 ANSWER 17 OF 22 CAPLUS COPYRIGHT 2004 ACS on STN
AU Nelson, David T.; Goodchild, Nancy L.; Mager, Dixie L.
TI Gain of Sp1 sites and loss of repressor sequences associated with a young, transcriptionally active subset of HERV-H endogenous long terminal repeats
SO Virology (1996), 220(1), 213-218
CODEN: VIRLAX; ISSN: 0042-6822
AB HERV-H sequences comprise a large family of human endogenous retrovirus-like elements. Previous DNA sequence comparisons of HERV-H long terminal repeats (LTRs) have led to their classification into three subtypes, Types I, Ia, and II. Type Ia appears to have been generated by recombination between Type I and Type II LTRs. These subtypes differ in evolutionary age and transcriptional activity with Type Ia LTRs being younger in evolutionary terms and possessing stronger promoter function than the other two subtypes. In this study, possible mechanisms responsible for the functional difference between LTRs have been explored. Types I and II LTRs each contain different sets of repeated segments in their U3 regions which are disrupted in Type Ia LTRs. Using reporter gene assays, we have shown that both types of repeated segments can suppress activity of the human β-globin gene promoter when cloned at a distant site. Both sets of repeats also repress promoter activity of a Type Ia LTR when directly inserted within its U3 region. In addition, using deletion constructs, we have localized two pos. regulatory segments within the Type Ia LTR, both of which contain a potential binding site for the

transcription factor Sp1. Gel mobility shift assays demonstrated that fragments containing these sites do bind Sp1. Although Type I LTRs are generally similar to Type Ia LTRs in the regions surrounding the Sp1 sites, there are sequence differences within the sites. Gel-shift anal. revealed no or much reduced Sp1 binding of Type I LTR fragments containing these sites. Thus, it appears that the loss of repeated suppresser elements and the acquisition of Sp1-binding sites have both contributed to the relatively strong transcriptional activity of the type Ia LTRs.

L2 ANSWER 18 OF 22 MEDLINE on STN DUPLICATE 7
AU Sjottem E; Anderssen S; Johansen T
TI The promoter activity of long terminal repeats of the HERV-H family of human retrovirus-like elements is critically dependent on Sp1 family proteins interacting with a GC/GT box located immediately 3' to the TATA box.
SO Journal of virology, (1996 Jan) 70 (1) 188-98.
Journal code: 0113724. ISSN: 0022-538X.
AB The HERV-H family of endogenous retrovirus-like elements is widely distributed in the human genome, with about 1,000 full-length elements and a similar number of solitary long terminal repeats (LTRs). HERV-H LTRs have been shown to direct the transcription of both HERV-H-encoded and adjacent cellular genes. Transcripts of HERV-H elements are especially abundant in placenta, teratocarcinoma cell lines, and cell lines derived from testicular and lung tumors. Here we report that only a subset of **HERV**-H LTRs display **promoter** activity in human cell lines and that these LTRs are characterized by the presence of a GC/GT box immediately downstream of the TATA box. This GC/GT box is required for promoter activity, while, surprisingly, the TATA box is dispensable. The ubiquitously expressed transcription factors Sp1 and Sp3 bound to this GC/GT box and stimulated transcription from the promoter-active LTRs in the teratocarcinoma cell line NTera2-D1. However, in HeLa and Drosophila SL-2 cells, Sp1 acted as a transcriptional activator of the LTRs, while Sp3 acted as a repressor of Sp1-mediated transcriptional activation. Cotransfection studies also revealed that the tissue-specific Sp1-related protein BTEB bound to this GC/GT box and stimulated transcription from the LTR promoters in NTera2-D1 cells. These results show that members of the Sp1 protein family are crucial determinants for transcriptional activation of **HERV**-H LTR **promoters** and suggest that these proteins may also be involved in determining the tissue-specific expression pattern of HERV-H elements.

L2 ANSWER 19 OF 22 CAPLUS COPYRIGHT 2004 ACS on STN
AU Strazzullo, Maria; Majello, Barbara; Lania, Luigi; La Mantia, Girolama
TI Mutational analysis of the human endogeneous ERV9 proviruses promoter region
SO Virology (1994), 200(2), 686-95
CODEN: VIRLAX; ISSN: 0042-6822
AB ERV9 is a low repeated family of human endogenous retroviral elements whose expression is mainly detectable in undifferentiated embryonal carcinoma NT2/D1 cells. To define all the elements required for the correct transcription activity of the ERV9 promoter and to establish a precise correlation between the elements important for basal transcription, the authors have systematically analyzed the in vivo and in vitro transcriptional activity of many different ERV9 promoter mutants, including a series of linker-scanning mutations across the promoter region. The authors report here that the ERV9 promoter contains two elements controlling the selection of the correct start sites, a TATA box and an Inr-like region; the concerted action of both elements is necessary for faithful transcription. Finally, using a series of GAL4 protein fusion constructs in cotransfection expts., the authors demonstrated that various transcription factors can synergistically induce a high level of transcription when bound to an ERV9 DNA promoter.

L2 ANSWER 20 OF 22 CAPLUS COPYRIGHT 2004 ACS on STN

AU La Mantia, Girolama; Majello, Barbara; Di Cristofano, Antonio; Strazzullo, Maria; Minchiotti, Gabriella; Lania, Luigi
TI Identification of regulatory elements within the minimal promoter region of the human endogenous ERV9 proviruses: accurate transcription initiation is controlled by an Inr-like element
SO Nucleic Acids Research (1992), 20(16), 4129-36
CODEN: NARHAD; ISSN: 0305-1048
AB ERV9 is a low repeated family of human endogenous retroviral elements whose expression is mainly detectable in undifferentiated embryonal carcinoma NT2/D1 cells. In this report the minimal promoter region located within the ERV9 LTR was analyzed. Using the transient CAT expression assay the minimal promoter region was identified and includes sequences spanning from -70 to +6 relative to the major transcription start site. Deletion anal., primer extension mapping of the transcription start sites and DNA-protein interactions assays permitted definition of two important regions within the ERV9 minimal promoter. One region located between -70 to -39 acts as a transcriptional activating sequence and contains an Sp1 binding site. The second region from -7 to +6, which resembles an initiator element (Inr), was necessary for the correct transcription start site utilization, and binds to a regulatory protein. Cross-competition expts. using various Inr elements have indicated that the protein that binds to the ERV9 Inr element can be competed by the HIV-1 and TdT Inr sequences.

L2 ANSWER 21 OF 22 CAPLUS COPYRIGHT 2004 ACS on STN
AU Ting, Chao Nan; Rosenberg, Michael P.; Snow, Claudette M.; Samuelson, Linda C.; Meisler, Miriam H.
TI Endogenous retroviral sequences are required for tissue-specific expression of a human salivary amylase gene
SO Genes & Development (1992), 6(8), 1457-65
CODEN: GEDEEP; ISSN: 0890-9369
AB The human salivary amylase genes are associated with two inserted elements, a γ-actin-processed pseudogene and an endogenous retroviral-like element. To test the contribution of these inserted elements to tissue specificity, 25 lines of transgenic mice carrying 10 amylase constructs were established. A 1-kb fragment of AMY1C (-1003 to +2) was found to be sufficient for parotid-specific expression of a human growth hormone reporter gene. The 1-kb fragment is entirely derived from inserted sequences. Deletion from -1003 to -826 resulted in reduced levels of transgene expression and loss of tissue-specificity. The fragment -1003 to -327 was sufficient to transfer parotid specificity to the thymidine kinase promoter. The data demonstrate that the functional tissue-specific promoter of human AMY1C is derived from inserted sequences and that parotid expression can be conferred by sequences derived solely from the retrovirus. A role for retrotranposition in the evolution of gene regulation is indicated by these and other recent observations.

L2 ANSWER 22 OF 22 CAPLUS COPYRIGHT 2004 ACS on STN
AU La Mantia, Girolama; Maglione, Domenico; Pengue, Gina; Di Cristofano, Antonio; Simeone, Antonio; Lanfrancone, Luisa; Lania, Luigi
TI Identification and characterization of novel human endogenous retroviral sequences prefentially expressed in undifferentiated embryonal carcinoma cells
SO Nucleic Acids Research (1991), 19(7), 1513-20
CODEN: NARHAD; ISSN: 0305-1048
AB A novel endogenous retroviral sequence (ERV-9) has been isolated from a human embryonal carcinoma cDNA library by hybridization to a probe containing a recently described human repetitive element. DNA sequence anal. of the 4kb cDNA insert (pHE.1) revealed the presence of ORFs potentially coding for putative retrovirus-related gag, pol, and env proteins. Northern blot and RNase protection expts. showed that RNA homologous to the pHE.1 insert is detected only in embryonal carcinoma cells as an 8 kb mRNA, and its expression is neg. regulated during retinoic acid induced differentiation of the human teratocarcinoma cell line NT2/D1. Using a pol specific

probe, a genomic locus containing the ERV-9 sequences was isolated. Characterization by restriction enzyme anal. and DNA sequencing allowed for definition of LTR-like sequences, that are composed of a complex array of subrepetitive elements. In addition the ERV-9 LTR sequences are able to drive expression of a linked CAT gene in a cell specific manner as LTR promoter activity has been detected only in NT2/D1 cells.

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